

This Page Is Inserted by IFW Operations  
and is not a part of the Official Record

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning documents *will not* correct images,  
please do not report the images to the  
Image Problem Mailbox.**

## WHAT IS CLAIMED IS:

1. A method for predicting the epidemic character of a *Mycobacterium tuberculosis* isolate and/or a selective advantage to be maintained in the host and/or the acquisition of multiple drug resistance (MDR) by the isolate, wherein the method comprises detecting an alteration in the DNA repair system of said isolate.
2. The method as claimed in claim 1, wherein the isolate contains a mutation in one or more *mutT* locus.
3. The method as claimed in claim 2, wherein the isolate consists essentially of a Beijing *Mycobacterium tuberculosis* strain.
4. The method as claimed in claim 3, wherein the isolate contains a mutation in one or more *mutT* family member selected from the Rv3908 locus, the *mutT2* locus, and the *ogt* locus.
5. The method as claimed in claim 2, wherein the isolate contains a mutation in at least one locus selected from *rpoB*, *rpsL*, *rrs*, and *rpsL*.
6. A method for detecting a *Mycobacterium tuberculosis* strain having a multiple drug resistant (MDR) phenotype, wherein the method comprises detecting a mutation in the Rv3908 locus of the genome of said *Mycobacterium tuberculosis* strain.

7. The method as claimed in claim 6, which comprises detecting a mutation at codon 48 of the Rv3908 locus.
8. The method as claimed in claim 7, which comprises detecting GGG at codon 48.
9. The method as claimed in claim 8, wherein the isolate contains a mutation in at least one locus selected from the group consisting of *rpoB*, *rpsI*, *rrs*, or *rpsL*.
10. A method for detecting a *Mycobacterium tuberculosis* strain having a multiple drug resistance (MDR) phenotype, wherein the method comprises detecting a mutation in the *mutT2* locus of the genome of said *Mycobacterium tuberculosis* strain.
11. The method as claimed in claim 10, which comprises detecting a mutation at codon 58 of the *mutT2* locus.
12. The method as claimed in claim 11, which comprises detecting CGA at codon 58.
13. The method as claimed in claim 12, wherein the isolate contains a mutation in at least one locus selected from the group consisting of *rpoB*, *rpsI*, *rrs*, or *rpsL*.

14. A method for detecting a *Mycobacterium tuberculosis* strain having a multiple drug resistance (MDR) phenotype, wherein the method comprises detecting a mutation in the *ogt* locus of the genome of said *Mycobacterium tuberculosis* strain.
15. A method of detecting a *Mycobacterium tuberculosis* strain having a multiple drug resistance (MDR) phenotype, wherein the method comprises:
- (a) providing a biological sample suspected of containing *Mycobacterium tuberculosis*;
  - (b) amplifying nucleic acids in the sample using as a primer pair
    - (i) SEQ ID NO: 1, and  
SEQ ID NO: 2; or
    - (ii) SEQ ID NO: 3, and  
SEQ ID NO: 4; or
    - (iii) SEQ ID NO: 5, and  
SEQ ID NO: 6; or
    - (iv) SEQ ID NO: 7, and  
SEQ ID NO: 8; and
  - (c) detecting a mutation in the Rv3908 locus, or the *mutT2* locus, or the *ogt* locus, or the *alkA* locus of the *Mycobacterium tuberculosis*.
16. The method as claimed in claim 15, wherein the isolate consists essentially of a Beijing *Mycobacterium tuberculosis* strain.

17. The method as claimed in claim 16, wherein the isolate contains a mutation in one or more *mutT* family member selected from the Rv3908 locus, the *mutT2* locus, and the *ogt* locus.
18. The method as claimed in claim 15, wherein the isolate contains a mutation in at least one locus selected from the group consisting of *rpoB*, *rpsL*, *rrs*, or *rpsL*.
19. The method as claimed in claim 15, wherein step (c) comprises detecting a mutation in the Rv3908 locus of the genome of said *Mycobacterium tuberculosis* strain.
20. The method as claimed in claim 19, which comprises detecting a mutation at codon 48 of the Rv3908 locus.
21. The method as claimed in claim 20, which comprises detecting GGG at codon 48.
22. The method as claimed in claim 15, wherein step (c) comprises detecting a mutation in the *mutT2* locus of the genome of said *Mycobacterium tuberculosis* strain.
23. The method as claimed in claim 22, which comprises detecting a mutation at codon 58 of the *mutT2* locus.

24. The method as claimed in claim 23, which comprises detecting CGA at codon 58.
25. The method as claimed in claim 15, wherein step (c) comprises detecting a mutation in the *ogt* locus of the genome of said *Mycobacterium tuberculosis* strain.
26. A polynucleotide consisting of contiguous nucleotides of the Rv3908 locus of a *Mycobacterium tuberculosis* strain including codon 48 of said locus, or a polynucleotide fully complementary thereto.
27. The polynucleotide as claimed in claim 26, wherein codon 48 is GGG.
28. The polynucleotide as claimed in claim 26, which contains the complement of SEQ ID NO: 1, SEQ ID NO: 2, or both SEQ ID NOS: 1 and 2.
29. A polynucleotide consisting of contiguous nucleotides of the *mufT2* locus of a *Mycobacterium tuberculosis* strain including codon 58 of said locus, or a polynucleotide fully complementary thereto.
30. The polynucleotide as claimed in claim 29, wherein codon 48 is CGA.
31. The polynucleotide as claimed in claim 29, which contains the complement of SEQ ID NO: 3, SEQ ID NO: 4, or both SEQ ID NOS: 3 and 4.

32. A purified polynucleotide comprising a nucleotide sequence selected from:

- (A) SEQ ID NO: 1;
- (B) SEQ ID NO: 2;
- (C) SEQ ID NO: 3;
- (D) SEQ ID NO: 4;
- (E) SEQ ID NO: 5;
- (F) SEQ ID NO: 6;
- (G) SEQ ID NO: 7; and
- (H) SEQ ID NO: 8.

33. A purified polynucleotide that hybridizes specifically under stringent conditions with one or more polynucleotide sequence selected from SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8.

34. A kit for detecting *M. tuberculosis*, said kit comprising:

- (A) a polynucleotide probe according to claim 1; and
- (B) reagents to perform a nucleic acid hybridization reaction.

35. A kit for detecting *M. tuberculosis*, said kit comprising:

- (A) a primer pair according to claim 15; and
- (B) reagents to perform a nucleic acid amplification reaction.

36. An *E. coli* strain containing the plasmid pMYC2501 deposited at the C.N.C.M. on August 20, 2001, under Accession No. I-2711.
37. An *E. coli* strain containing the plasmid pMYC2502 deposited at the C.N.C.M. on August 20, 2001, under Accession No. I-2712.
38. An *E. coli* strain containing the plasmid pMYC2503 deposited at the C.N.C.M. on August 20, 2001, under Accession No. I-2713.
39. A purified polynucleotide sequence delimited upstream by the polynucleotide sequence of SEQ ID NO: 1 and downstream by the polynucleotide sequence of SED ID NO: 2, wherein the purified polynucleotide sequence comprises SEQ ID NO: 29.
40. A purified polynucleotide sequence delimited upstream by the polynucleotide sequence of SEQ ID NO: 3 and downstream by the polynucleotide sequence of SED ID NO: 4, wherein the purified polynucleotide sequence comprises SEQ ID NO: 30.
41. A purified polynucleotide sequence delimited upstream by the polynucleotide sequence of SEQ ID NO: 5 and downstream by the polynucleotide sequence of SED ID NO: 6, wherein the purified polynucleotide sequence comprises SEQ ID NO: 27.



42. A purified polynucleotide sequence delimited upstream by the polynucleotide sequence of SEQ ID NO: 7 and downstream by the polynucleotide sequence of SEQ ID NO: 8, wherein the purified polynucleotide sequence comprises SEQ ID NO: 28.

43. A purified polynucleotide sequence originating from a gene of *M. tuberculosis* comprising a mutator allele.

44. A method for detecting in a patient infected by *M. tuberculosis* a higher risk of being unable to eliminate the bacillus or of being able to develop MDR tuberculosis, wherein the method comprises detecting the presence of mutator alleles in clinical strains of *M. tuberculosis* with one or more polynucleotide fragment selected from SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8.

45. A polynucleotide selected from:  
a polynucleotide fragment comprising SEQ ID NO: 1 (*mutT2-1*);  
a polynucleotide fragment comprising SEQ ID NO: 2 (*mutT2-2*);  
a polynucleotide fragment comprising SEQ ID NO: 3 (*Rv3908-1*);  
a polynucleotide fragment comprising SEQ ID NO: 4 (*Rv3908-2*);  
a polynucleotide fragment comprising SEQ ID NO: 5 (*alkA-1*);  
a polynucleotide fragment comprising SEQ ID NO: 6 (*alkA-2*);  
a polynucleotide fragment comprising SEQ ID NO: 7 (*ogt-1*);  
a polynucleotide fragment comprising SEQ ID NO: 8 (*ogt-2*);

a purified polynucleotide of 1488 bp designated as *alkA* and consisting of  
SEQ ID NO: 27;

a purified polynucleotide of 495 bp designated as *ogt* and consisting of SEQ  
ID NO: 28;

a purified polynucleotide of 423 bp designated *mutT2* and consisting of SEQ  
ID NO: 29;

a purified polynucleotide of 744 bp designated Rv3908 and consisting of SEQ  
ID NO: 30;

a purified polynucleotide of 912 bp designated *mutY* and consisting of SEQ ID  
NO: 31;

a purified polynucleotide of 2406 bp designated Rv3909 and consisting of  
SEQ ID NO: 32;

a purified polynucleotide comprising SEQ ID NO: 27 (*alkA*);

a purified polynucleotide comprising SEQ ID NO: 28 (*ogt*);

a purified polynucleotide comprising SEQ ID NO: 29 (*mutT2*);

a purified polynucleotide comprising SEQ ID NO: 30 (Rv3908);

a purified polynucleotide comprising SEQ ID NO: 31 (*mutY*); and

a purified polynucleotide comprising SEQ ID NO: 32 (Rv3909).